Clinical Trials Integrating Immunotherapy and Radiation for Non–Small-Cell Lung Cancer

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Abstract: Methods of harnessing the immune system to treat cancer have been investigated for decades, but yielded little clinical progress. However, in recent years, novel drugs that allow immune recognition and destruction of tumor cells are emerging as potent cancer therapies. Building upon previous immunotherapy strategies that included therapeutic vaccines, recombinant cytokines, and other immunostimulatory agents, newer immunotherapy agents targeting immune checkpoints including programmed cell death 1, programmed cell death ligand-1, and cytotoxic T-lymphocyte-associated protein 4, among others, have garnered substantial enthusiasm after demonstrating clinical activity in a broad spectrum of tumor types. Trials evaluating immune checkpoint inhibitors in metastatic non–small-cell lung cancer (NSCLC) demonstrate robust and durable responses in a subset of patients. However, with overall response rates less than 20%, combinatorial strategies that extend the benefit of these agents to more patients are desirable. The integration of radiotherapy with immunotherapy is a conceptually promising strategy, as radiotherapy has potent immunomodulatory effects and may contribute not only to local control but may also augment systemic antitumor immune response. Preclinical data and case reports suggest the potential for robust clinical responses in metastatic NSCLC patients using this strategy, but prospective clinical trials evaluating the integration of radiation and immunotherapy are limited. The use of immunotherapy in nonmetastatic settings is also intriguing but understudied. We review the potential clinical settings of interest for the partnering of immunotherapy and radiation in NSCLC, including early stage, locally advanced, and metastatic disease, and review completed, accruing, and developing clinical trials.

Key Words: Non–small-cell lung cancer, Immunotherapy, Radiotherapy.

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Lung cancer has traditionally been characterized as insensitive to immune strategies. The first randomized trials to evaluate immunotherapy date back to the 1970s with the instillation of adjuvant intrapleural BCG.[1,2] Although BCG was ineffective, the pursuit of an immune agent to treat lung cancer continued. Phase III trials evaluating interferon and a variety of vaccines, however, were unsuccessful.[3,4] Meanwhile, dramatic advances in our understanding of the molecular mechanisms of tumor immunology, now known as the cancer-immunity cycle, have allowed for the development of new drugs and improved vaccines and cellular therapies, reigniting enthusiasm for immunotherapy of lung cancer.[5] Most exciting is the new class of agents called immune checkpoint inhibitors. Checkpoint inhibitors targeting programmed cell death 1 (PD-1), programmed cell death ligand-1 (PD-L1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and others have demonstrated clinical efficacy in a broad spectrum of tumor types, with pronounced and durable remissions in a subset of patients. In lung cancer, PD-1 and PD-L1 inhibitors as monotherapy for metastatic non–small-cell lung cancer (NSCLC) have shown response rates of 15% to 20%, with typically dramatic and durable results in both nonsquamous and squamous histologies.[6–8] A recently published phase III trial comparing the anti-PD-1 monoclonal antibody nivolumab to docetaxel as second-line treatment for advanced squamous NSCLC demonstrated superior median survival of 9.2 months (95% confidence interval [CI]: 7.3–13.3) with nivolumab as compared with 6.0 months (95% CI: 5.1–7.3) with docetaxel,[9] and a parallel study identified superior median survival of 12.2 months (95% CI: 9.7, 15.0) for nivolumab versus 9.4 months (95% CI: 8.0, 10.7) with docetaxel for nonsquamous histology (hazard ratio = 0.73; 96% CI: 0.59, 0.89; $p = 0.00155$).[10] Nivolumab was recently FDA approved for the second-line treatment of advanced stage patients with squamous histology.[11]

There is substantial interest in extending the benefit of immune checkpoint inhibitors to a greater proportion to patients. Efforts are underway to develop combined modality strategies, including dual immunotherapies, integration of chemotherapy and targeted therapies, and combination with radiotherapy. Radiotherapy is a particularly appealing partner therapy, offering the benefit of a generally nonoverlapping toxicity profile, with both preclinical and early clinical data suggesting potential potent immunostimulatory effects. Radiotherapy induces multiple immunomodulatory changes that can potentially influence the effectiveness of immunotherapy including tumor vasculature normalization,[12] improved T-cell extravasation and

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homing to tumors,[12] destruction of immunosuppressive stromal cells,[13] induction of immunogenic tumor cell death via high mobility group protein B1 release,[14] or exposure of calreticulin on the cell surface,[15] among others (Table 1, Fig. 1). Clinical support for an interaction between radiotherapy and the immune response is demonstrated by the abscopal (*ab-scopus*, away from the target) effect, in which a systemic tumor response is observed after local radiation.[24] Although once thought to be an infrequent event, increasing reports of an abscopal effect with the combination of immune checkpoint inhibitors and radiation have renewed our interest in this phenomenon and justify the evaluation of immunoradiotherapy strategies.[25]

Clinical studies evaluating immunotherapy and radiation for NSCLC have focused on metastatic disease. However, other settings, including early stage and locally advanced disease, are also intriguing. The effects of immunotherapy may be best suited to eradication of micrometastases, suggesting neoadjuvant, concurrent, or adjuvant immunotherapy strategies in the localized setting should be further explored. We review a representative sample of completed, ongoing, and developing clinical trials evaluating the combination of radiotherapy and immunotherapy for NSCLC, and suggest areas for future investigation.

TABLE 1. Mechanisms of Radiation-Induced Immune Modulation

Tumor debulking and releasing tumor antigens	
Not systemically immunosuppressive	
Up-regulation of immunogenic cell surface markers	
ICAM-1	Chakraborty et al.[16]
MHC-1	Formenti et al.[17]
Fas	Chakraborty et al.[16]
Secretion of danger signals and cytokines	
IFN-g	Lugade et al.[18]
TNFa	Formenti et al.[17]
IL-1b	Formenti et al.[17]
Induction of immunogenic cell death	
Calreticulin	Obeid et al.[19]
HMGB1	Apetoh et al.[14]
Increased homing of immune cells to tumors	
Normalization of tumor vasculature	Ganss et al.[20]
Secretion of chemo-attractants (cxcl16)	Matsumura et al.[21]
Endothelial expression of VCAM-1	Lugade et al.[18]
Improved T-cell homing to tumors	Klug et al.[12]
Improved antigen presentation by APC's	
Irradiated tumors prime dendritic cells	Strome et al.[22]
Improved antigen presentation via TLR-4	Apetoh et al.[14]
Depletion of immunosuppressive cells	Wu et al.[13]
Shifting TAM polarization to M1	Klug et al.[12]
Up-regulation of cell surface PD-L1	Dovedi et al.[23]

MHC-1, major histocompatibility complex 1; HMGB-1, high mobility group protein B1; VCAM, Vascular Cell Adhesion Protein-1; APC, Antigen-presenting cell; TLR-4, toll-like receptor; TAM, tumor-associated macrophage; PD-L1, programmed cell death ligand-1.

IMMUNOTHERAPY AND RADIATION IN METASTATIC NSCLC

Rationale

Early combinatorial strategies for radiotherapy and immunotherapy in NSCLC have logically focused on patients with metastatic disease, a patient population with a dismal median survival of 10 to 12 months and few efficacious treatment strategies beyond first-line chemotherapy.[26] Important questions include not only the efficacy of radiation–immunotherapy combinations, patient selection, and choice of immunotherapy agent(s), but also the optimal sequencing, radiotherapy dose/fractionation, disease burden at treatment, and impact of potentially immunosuppressive prior therapies. Relatively few studies have been completed, but substantial enthusiasm for these agents has led to a number of accruing and developing clinical trials. Many currently accruing trials combine immunotherapy agents with stereotactic body radiotherapy (SBRT), a precise technique that allows delivery of high radiation doses over one to five fractions. The optimal dose and fractionation to best augment the antitumor immune response, however, is unclear. A study combining a toll-like receptor 7 agonist and local radiation in a murine lymphoma model found that 2 Gy ×5 fractions resulted in greater tumor response than the toll-like receptor 7 agonist and a single 10 Gy fraction.[27] Similarly, a study using a breast cancer murine model found that anti-CTLA-4 therapy combined with fractionated radiation (8 Gy ×3 or 6 Gy ×5) resulted in abscopal tumor responses while the same immunotherapy combined with 20 Gy ×1 did not generate a systemic response.[28] By contrast, a study using a murine melanoma model found that a single dose of 20 Gy better promotes priming of antigen-specific cells than 4 Gy ×5, and that 12 Gy ×2 combined with intratumoral injections of a T cell therapy resulted in prolonged survival and prevented metastases.[29] Other work in murine melanoma models suggests a moderate, hypofractionated regimen using 7.5 Gy fractions may optimize tumor control, antitumor immunity, and minimize the contribution of regulatory T cells.[30] Similar studies specific to lung cancer models are lacking.

Completed and Currently Accruing Clinical Studies in Metastatic Disease

Trials combining immune checkpoint inhibitors with radiotherapy are ongoing or planned as shown in Table 2. After noting a durable complete systemic response in a NSCLC patient treated with ipilimumab plus SBRT to a liver lesion, investigators at New York University have activated a phase I/II study evaluating ipilimumab delivered at 3 mg/kg IV combined with SBRT to 30 Gy over five fractions to a single metastasis for stage IV NSCLC[31,32] (NCT02221739). SBRT and ipilimumab begin within a 24-hour interval, and ipilimumab is repeated every 21 days for up to four cycles. The primary outcome measure is tumor response by the immune-related response evaluation criteria in solid tumors[33] outside the radiation field.

A second accruing study evaluates radiotherapy and ipilimumab for metastatic solid tumors, including NSCLC. Investigators at the MD Anderson Cancer Center have activated a phase I/II trial enrolling patients with metastatic solid